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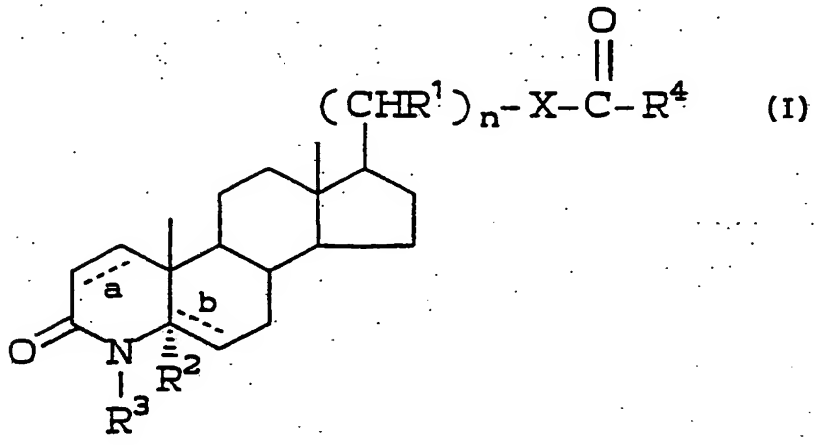

(57) Abstract

Compounds of formula (I), wherein X is sulfur or oxygen are inhibitors of the 5α-reductase enzyme and isozymes thereof. The compounds are useful for the treatment of hyperandrogenic disease conditions and diseases of the skin and scalp.

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TITLE OF THE INVENTION

ESTER DERIVATIVES OF 4-AZA-STEROIDS

BACKGROUND OF THE INVENTION

The present invention is directed to new 17-position ester and thioester derivatives of 4-azaandrostan-3-ones and related compounds and the use of such compounds as 5α-reductase inhibitors.

The art reveals that certain undesirable physiological manifestations, such as acne vulgaris, seborrhea, female hirsutism, male pattern baldness and benign prostatic hypertrophy, are the result of hyperandrogenic stimulation caused by an excessive accumulation of testosterone or similar androgenic hormones in the metabolic system. Early attempts to provide a chemotherapeutic agent to counter the undesirable results of hyperandrogenicity resulted in the discovery of several steroidal antiandrogens having undesirable hormonal activities of their own.

The estrogens, for example, not only counteract the effect of the androgens but have a feminizing effect as well. Non-steroidal antiandrogens have also been developed, for example, 4'-nitro-3'-trifluoromethyl-isobutyranilide. See Neri, et al., Endo., Vol. 91, No. 2 (1972). However, these products, though devoid of hormonal effects, are peripherally active, competing with the natural androgens for receptor sites, and hence have a tendency to feminize a male host or the male fetus of a female host.

It is now known in the art that the principal mediator of androgenic activity in some target organs is 5α-dihydrotestosterone, and that it is formed locally in the target organ by the action of testosterone-5α-reductase. It is also known that inhibitors of testosterone-5α-reductase will serve to prevent or lessen symptoms of hyperandrogenic stimulation.

A number of 4-aza steroid compounds are known in the art as 5α-reductase inhibitors. For example, See U.S. Patent Nos. 2,227,876, 3,239,417, 3,264,301 and 3,285,918; French Patent No. 1,465,544; Doorenbos and Solomons, J. Pharm. Sci. 62, 4, pp. 638-640 (1973); Doorenbos and Brown, J. Pharm. Sci., 60, 8, pp. 1234-1235 (1971); and Doorenbos and Kim, J. Pharm. Sci. 63, 4, pp. 620-622 (1974).

In addition, U.S. Patent Nos. 4,377,584, 4,220,775, 4,859,681, 4,760,071 and the articles J. Med. Chem. 27, p. 1690-1701 (1984) and J. Med. Chem. 29, 2998-2315 (1986) of Rasmusson, et al., U.S.

Patent 4,845,104 to Carlin, et al., and U.S. Patent 4,732,897 to Cainelli, et al. describe 4-aza-17ß-substituted-5α-androstan-3-ones which are said to be useful in the treatment of DHT-related hyperandrogenic conditions.

However, despite the suggestion in the prior art that hyperandrogenic diseases are the result of a single 5α-reductase, there are reports regarding the presence of other 5α-reductase isozymes in both rats and humans. For example, in human prostate, Bruchovsky, et al. (See J. Clin. Endocrinol. Metab. 67, 806-816, 1988) and Hudson (see J. Steroid Biochem. 26, p 349-353, 1987) found different 5α-reductase activities in the stromal and epithelial fractions. Additionally, Moore and Wilson described two distinct human reductases with peaks of activities at either pH 5.5 or pH 7-9. (See J. Biol. Chem. 251, 19, p. 5895-5900, 1976.)

Recently, Andersson and Russell isolated a cDNA which encodes a rat liver 5α-reductase (see J. Biol. Chem. 264 pp. 16249-55 (1989). They found a single mRNA which encodes both the liver and prostatic reductases of rats. The sequence of this rat gene was later used to select a human prostatic cDNA encoding a 5α-reductase termed "5α-reductase 1". (See Proc. Nat'l. Acad. Sci. 87, p. 3640-3644, 1990.)

More recently, a second, human prostatic reductase (5α-reductase 2) has been cloned with properties identified with the more abundant form found in crude human prostatic extracts. (See Nature, 354, p. 159-161, 1991.)

Further, "Syndromes of Androgen Resistance" - The Biology of Reproduction, Vol. 46, p. 168-173 (1992) by Jean O. Wilson indicates that the 5α-reductase 1 enzyme may be associated with hair follicles.

Thus, the art supports the existence of at least two genes for 5α-reductase and two distinct isozymes of 5α-reductase in humans. Both forms are present in prostatic tissue in which, 5α-reductase 2, is the more abundant, and the other isozyme, 5α-reductase 1, is believed to be more abundant in scalp tissue.

In the treatment of hyperandrogenic disease conditions, e.g. benign prostatic hyperplasia (BPH), it would be desirable to have one drug entity which is active against both enzymes 1 and 2 in the prostate to substantially inhibit dihydrotestosterone (DHT) production. Alternatively, it would be desirable to have a drug entity which is highly selective for inhibiting the scalp associated enzyme 5α-reductase 1, for use in treating diseases of the skin and scalp, e.g. acne and alopecia. The drug could also be used in combination with PROSCAR® (finasteride) which is highly selective for the prostatic enzyme 5α-reductase 2 for combination therapy in the treatment of BPH.

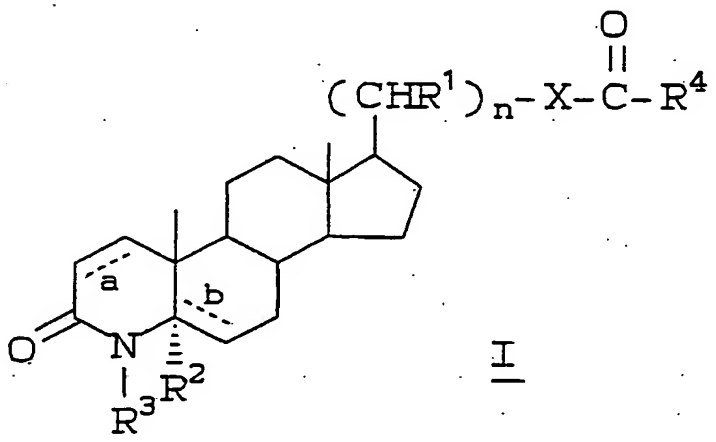
SUMMARY OF THE INVENTION

The present invention discloses novel 17-position ester and thioester derivatives of 4-azaandrostan-3-ones and related compounds which are

useful for inhibiting the steroid 5α-reductase enzymes 1 and 2. The compounds are particularly effective in selectively inhibiting the 5α-reductase 1 associated with the scalp, and dually inhibiting both isozymes 1 and 2 in the oral, parenteral or topical treatment of benign prostatic hyperplasia, acne, female hirsutism, male pattern baldness, androgenic alopecia, prostatitis, and the prevention and treatment of prostatic carcinoma.

DETAILED DESCRIPTION

This invention is concerned with compounds of formula I, and combinations thereof for the selective inhibition of 5α-reductase 1 and the combined inhibition of 5α-reductase 1 and 2. Compounds of formula I are defined as follows:



I

wherein a and b are both single bonds and R^2 is hydrogen, or

a is a double bond, b is a single bond and R^2 is hydrogen, or

a is a single bond, b is a double bond and R^2 is absent;

R^1 is -H, aryl, or $-C_{1-3}$alkyl unsubstituted or substituted with aryl and can be the same or different at each occurrence when n is greater than 1;

R^3 is -H, methyl, ethyl, -OH, $-NH_2$ or $-SCH_3$;

n is an integer selected from zero through 10;

X is -O- or -S-; and

R^4 is 1) $-C_{1-20}$ alkyl, unsubstituted or substituted with one or more of:

a) -OH,

b) halo,

c) $-C_{1-8}$ alkoxy,

d) $-C_{1-6}$ alkenyl,

e) $-CONR^5R^5$, wherein R^5 is independently

i) -H,

ii) $-C_{1-8}$ alkyl unsubstituted or substituted with one or more of R^7, aryl or heterocycle, the aryl being unsubstituted or substituted with one or more of R^7 or R^9,

iii) aryl unsubstituted or substituted with one or more of R^7 or R^9, or

iv) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9,

f) $-COOR^6$, wherein R^6 is

i) -H,

ii) $-C_{1-8}$ alkyl unsubstituted or substituted with one or more of R^7 or aryl, the aryl being unsubstituted or substituted with one or more of R^7 or R^9, or

iii) aryl, unsubstituted or substituted with one or more of R^7 or R^9,

g) $-S(O)_p-R^5$, wherein p is zero, 1 or 2;

h) $-N(R^5)_2$,

i) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9,

j) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9,

k) $-C_{3-10}$ cycloalkyl, such as cyclohexyl, norbornyl, or adamantyl, unsubstituted or substituted with one or more of R^7 or R^9, or

l) $-CONR^8-CO-NHR^8$, wherein R^8 is -H, $-C_{1-8}$ alkyl, benzyl or cyclohexyl,

2) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9,

3) heterocycle or $-C_{3-10}$ cycloalkyl, either of which is unsubstituted or substituted with one or more of R^7 or R^9,

4) $-NR^5R^5$, or

5) $-OR^5$;

R^7 is
1) -OH,
2) $-C_{1-3}$ alkoxy,
3) -CN,
4) $-COOR^6$
5) $-C_{1-8}$alkyl-$COOR^6$
6) $-NO_2$, or
7) halo; and
8) amino, mono-C_1-C_4alkylamino, di-C_1-C_4-alkylamino;

R^9 is
1) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or more of aryl or R^7,
2) -CO-A, $-C_{1-8}$ alkyl-CO-A, -NHCO-A, or $-S(O)_p$-A, wherein p is defined above and A is
a) -H,
b) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or more of
i) $-R^7$, or
ii) aryl, unsubstituted or substituted with one or more of R^7, or
c) aryl, unsubstituted or substituted with one or more of R^7,
3) -NHCO-heterocycle,
4) $-N(R^{10})_2$ or $-CON(R^{10})_2$ wherein R^{10} is independently, heterocycle or -A,
5) $-NHCO-(CH_2)_q-CO-Q$, wherein q is 1-4, and Q is $-N(R^{10})_2$ or $-OR^{10}$;

with the provisos that:

when n is 1-10, b is a single bond, R^1 is -H at each occurrence, X is -O-, and R^4 is $-C_{1-6}$alkyl, R^4 is not substituted with an unsubstituted phenyl ring;

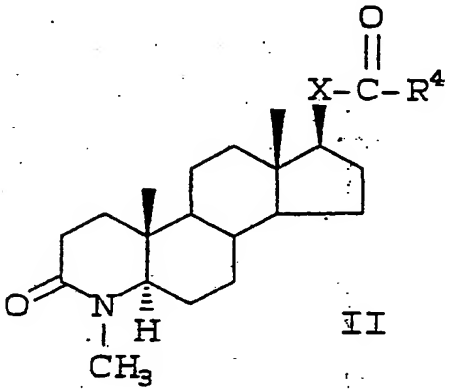
when n is 1-10, b is a single bond, R^1 is -H at each occurrence, and X is -O-, R^4 is not unsubstituted C_{5-10}cycloalkyl, unsubstituted phenyl, amino, $-C_{1-8}$alkyl substituted amino, or $-C_{1-8}$alkoxy;

when n is zero, X is -O-, a and b are both single bonds and R^3 is -H, then R^4 is not $-CH_3$; and

when n is 1, R^1 is $-CH_3$, X is -O-, a and b are both single bonds, and R^3 is -H, then R^4 is not $-CH_3$;

or a pharmaceutically acceptable salt or ester thereof.

A first preferred embodiment of this invention is represented by compounds of formula II



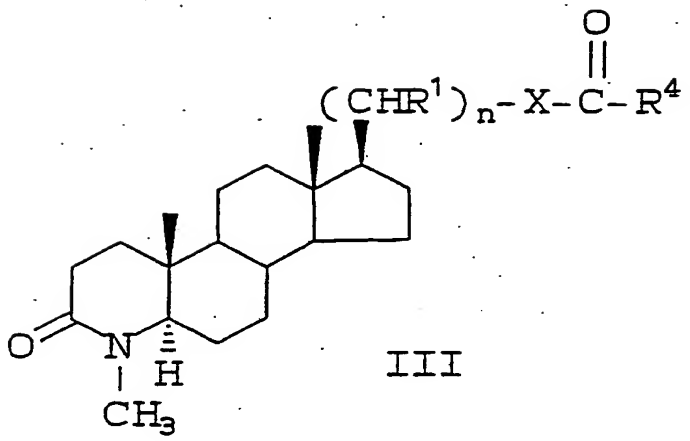
II

wherein R^4 is $-C_{1-20}$alkyl, unsubstituted or substituted with one or more of
-OH, halo, $-C_{1-8}$alkoxy, $-C_{1-6}$alkenyl, $-S(O)_p-R^5$, $-N(R^5)_2$, aryl unsubstituted or substituted with one or more of aryl, R^7or R^9, heterocycle unsubstituted or substituted with one or more of R^7 or R^9, or $-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9, and X, p, R^5, R^7, and R^9 are all as defined in formula I.

A second preferred embodiment of this invention is represented by compounds of formula II wherein R^4 is $-C_{1-20}$ alkyl substituted with $-CONR^5R^5$, $-COOR^6$ or $-CONR^8CONHR^8$, and X, R^5, R^6, and R^8 are all as defined in formula I.

A third preferred embodiment of this invention is represented by compounds of formula II wherein R^4 is
aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9;
heterocycle unsubstituted or substituted with one or more of R^7 or R^9;
$-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9;
$-NR^5R^5$; or $-OR^5$;
and X, R^5, R^7, and R^9 are all as defined in formula I.

A fourth preferred embodiment of this invention is represented by compounds of formula III



III

wherein R^4 is $-C_{1-20}$ alkyl, unsubstituted or substituted with one or more of
$-OH$, halo, $-C_{1-8}$alkoxy, $-C_{1-6}$alkenyl, $-S(O)_p-R^5$, $-N(R^5)_2$, aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9, heterocycle unsubstituted or substituted with one or more of R^7 or R^9, or $-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9,
and X, n, p, R^1, R^5, R^7, and R^9 are all as defined in formula I.

A fifth preferred embodiment of this invention is represented by compounds of formula III wherein R^4 is $-C_{1-20}$ alkyl substituted with $-CONR^5R^5$, $-COOR^6$ or $-CONR^8CONHR^8$,
and X, n, R^1, R^5, R^6, and R^8 are all as defined in formula I.

A sixth preferred embodiment of this invention is represented by compounds of formula III wherein R^4 is

aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9;

heterocycle unsubstituted or substituted with one or more of R^7 or R^9;

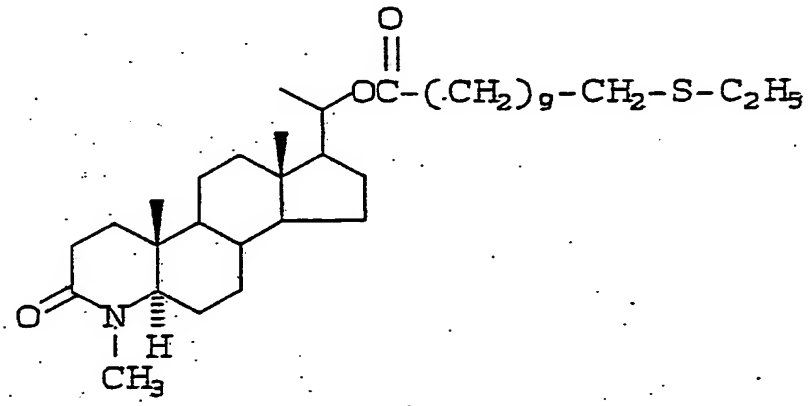
$-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9;

$-NR^5R^5$; or $-OR^5$;

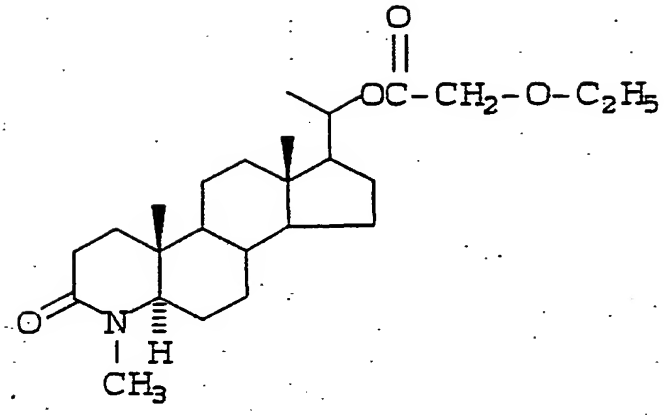
and X, n, R^1, R^5, R^7, and R^9 are all as defined in formula I.

Unless other wise specified, the 17-substituent is assumed to be in the beta configuration.

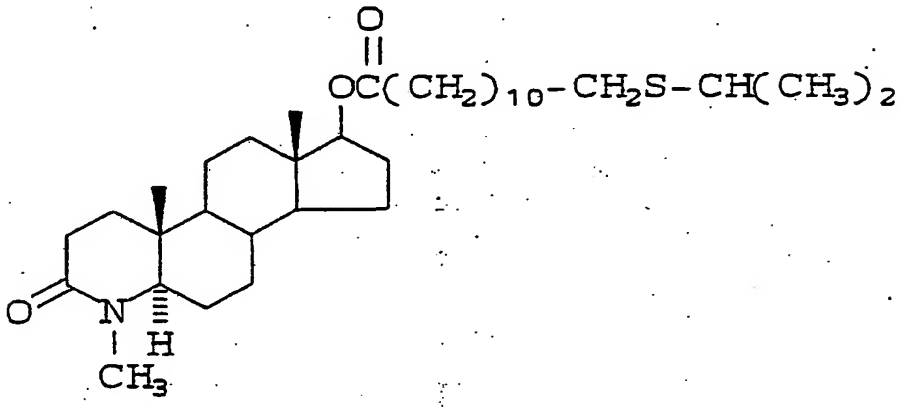
Novel compounds of the present invention include but are not limited to the following compounds:



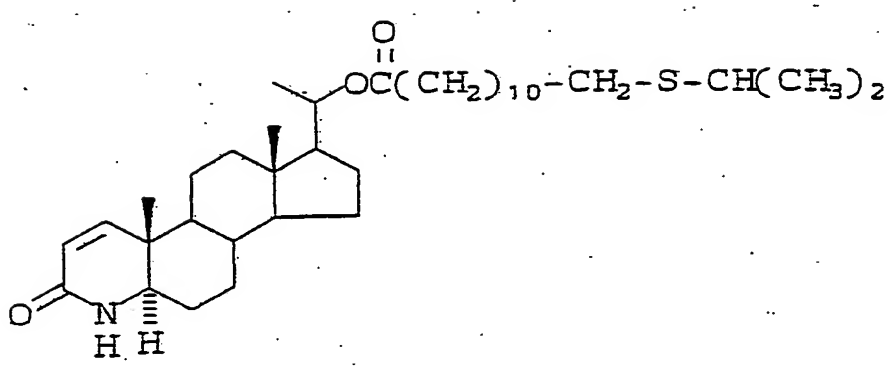
20-(11-(ethylthio)undecanoyloxy)-4-methyl-5α-4-azapregnan-3-one,



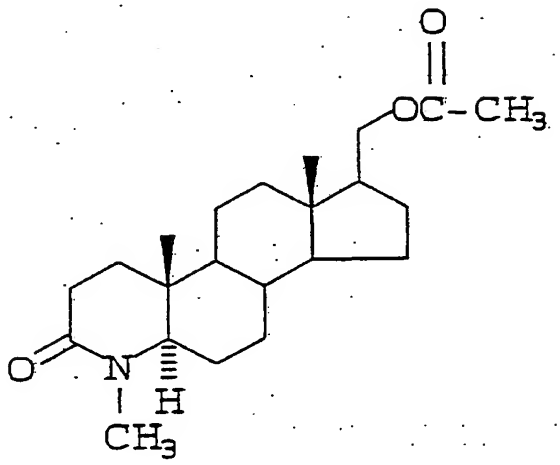
20-ethoxyacetyloxy-4-methyl-5α-4-azapregnan-3-one,



17-(12-(isopropylthio)dodecanoyloxy)-4-methyl-5α-4-azaandrostan-3-one,



20-(12-(isopropylthio)-dodecanoyloxy)-5α-4-azapregn-1-ene-3-one,



17-acetyloxymethyl-4-methyl-5α-4-azaandrostan-3-one,

4-methyl-20-tridecanoyloxy-5α-4-azapregnan-3-one,
20-t-butylacetyloxy-4-methyl-5α-4-azapregnan-3-one,
4-methyl-20-trimethylacetyloxy-5α-4-azapregnan-3-one,
4-methyl-20-(10-undecenoyloxy)-5α-4-azapregnan-3-one,
20-(3,7-dimethyl-6-octenoyloxy)-4-methyl-5α-aza-pregnan-3-one,
20-(3-carboxypropionyloxy)-4-methyl-5α-4-azapregnan-3-one,
20-(11-(carbomethoxy)undecanoyloxy)-4-methyl-5α-4-azapregnan-3-one,
20-(3-(carbobenzyloxy)propionyloxy)-4-methyl-5α-4-azapregnan-3-one,
20-(1-adamantylacetyloxy)-4-methyl-5α-4-azapregnan-3-one
4-methyl-20-(2-norbornylacetyloxy)-5α-4-azapregnan-3-one,
20-(3,4-dimethoxyphenyl)acetyloxy-4-methyl-5α-4-aza-pregnan-3-one,
20-(4-isopropylphenyl)acetyloxy-4-methyl-5α-4-aza pregnan-3-one
20-(isopropylthio)acetyloxy-4-methyl-5α-4-aza-pregnan-3-one,
20-(9-(isopropylthio)nonanoyloxy)-4-methyl-5α-4-aza-pregnan-3-one,
20-(12-(isopropylthio)dodecanoyloxy)-4-methyl-5α-4-azapregnan-3-one,

20-(11-(ethylsulfinyl)undecanoyloxy)-4-methyl-5α-4-azapregnan-3-one,
20-(12-(t-butylthio)dodecanoyloxy)-4-methyl-5α-4-azapregnan-3-one
4-methyl-20-(4-(thien-2-yl))butyroyloxy-5α-4-azapregnan-3-one,
20-trimethylacetyloxy-5α-4-azapregnan-3-one,
20-(9-(isopropylthio)nonanoyloxy)-5α-4-azapregnan-3-one,
20-(12-(isopropylthio)dodecanoyloxy)-5α-4-azapregnan-3-one,
20-acetoxymethyl-4-methyl-5α-4-azapregnan-3-one,
4-methyl-20-(trimethylacetyloxy)methyl-5α-4-azapregnan-3-one,
20-(12-(isopropylthio)dodecanoyloxy)methyl-4-methyl-5α-4-azapregnan-3-one,
4-methyl-17-trimethylacetyloxymethyl-5α-4-azaandrostan-3-one,
17-(2-ethylhexanoyloxy)methyl-4-methyl-5α-4-azaandrostan-3-one,
17-(12-(isopropylthio)dodecanoyloxy)methyl-4-methyl-5α-4-azaandrostan-3-one,
20-trimethylacetyloxy-5α-4-azapregn-1-ene-3-one,
17ß-(benzylaminocarbonyloxy)-4-methyl-5α-4-azaandrostan-3-one,
20-(t-butylaminocarbonyloxy)-4-methyl-5α-4-azapregnan-3-one,

17-(t-butylaminocarbonyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one or
17-(methylaminocarbonyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one.

Novel compounds of the present invention further include, but are not limited to the following compounds:
17-(2-furylacetoxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
17-(4-isopropylphenylacetoxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
17-(cyclohexylacetoxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
17-(3-indolylacetoxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
17-(4-methylcyclohexanecarbonyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
17-(4-(3-indolyl)-butyryloxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
17-(4-isobutylbenzoyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
17-(acetoxyacetyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
17-(6-bromohexanoyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
4-methyl-20-(4-nitrobenzoyloxymethyl)-5α-4-azapregnan-3-one,
20-((3-acetamido)benzoyloxy)-4-methyl-5α-4-azapregnan-3-one,

20-(3,4-dimethoxyphenylacetyloxymethyl)-4-methyl-5α-4-azapregnan-3-one,
17-(4-ethoxybenzoyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
4-methyl-20-(palmitoyloxymethyl)-5α-4-azapregnan-3-one,
17-(iminodibenzyl-5-carbonyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
4-methyl-20-(stearoyloxy)-5α-4-azapregnan-3-one,
17-(3,5-bis-(trifluoromethyl)benzoyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
17-(3-cyanobenzoyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
20-(heptafluorobutyryloxymethyl)-4-methyl-5α-4-azapregnan-3-one,
20-(4-benzoylbenzoyloxymethyl)-4-methyl-5α-4-azapregnan-3-one,
17-(benztriazol-5-carbonyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
20-(3,5-difluorobenzoyloxy)-4-methyl-5α-4-azapregnan-3-one,
17-(bis-(4-isopropyl)phenyl)acetyloxymethyl-4-methyl-5α-4-azaandrostan-3-one,
4-methyl-20-(salicylyloxymethyl)-5α-4-azapregnan-3-one,
17-((3-hydroxy-4,4,4-trichlorobutyryloxy)methyl)-4-methyl-5α-4-azaandrostan-3-one, or
17-(cinnamoyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one.

Also included within the scope of this invention are pharmaceutically acceptable salts or esters, where a basic or acidic group is present in a compound of formula I, such as on the substituted alkyl, cycloalkyl, aryl or heterocyclic moiety. When an acidic substituent is present, i.e. -COOH, there can be formed the ammonium, sodium, potassium, calcium salt, and the like, for use as the dosage form.

Where a basic group is present, i.e. amino, acidic salts, i.e. hydrochloride, hydrobromide, acetate, pamoate, and the like, can be used as the dosage form.

Also, in the case of the -COOH group being present, pharmaceutically acceptable esters can be employed, e.g. acetate, maleate, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

The compounds of the present invention, may have asymmetric centers and occur as racemates, racemic mixtures and as individual diastereomers, with all isomeric forms being included in the present invention.

When any variable (e.g., aryl, heterocycle, R^1, R^2, n, X, etc.) occurs more than one time in any constituent or in formula I, II or III its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein "alkyl" is intended to include both branched- and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms (Me is methyl, Et is ethyl, Pr is propyl, Bu is butyl); "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Cycloalkyl" is intended to include saturated mono-, bi- and tricyclic ring groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl (Cyh), cycloheptyl, norbornanyl and adamantyl. "Alkenyl" is intended to include hydrocarbon groups of either a straight or branched configuration with one or more carbon-carbon double bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, butenyl, pentenyl, and the like. "Halo", as used herein, means fluoro, chloro, bromo and iodo.

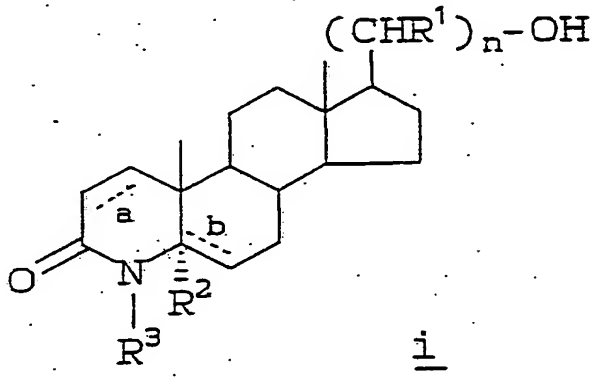
As used herein, with exceptions as noted, "aryl" is intended to mean phenyl (Ph) or naphthyl.

The term heterocycle or heterocyclic, as used herein except where noted, represents a stable 5- to 7-membered monocyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to three heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached

at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzopyranyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, and oxadiazolyl. Morpholino is the same as morpholinyl. Preferred heterocycles are piperidinyl, 2-oxopyrrolodinyl, pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, thiazolyl, isothiazolyl, quinuclidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, thiadiazoyl, benzothiazolyl, benzoxazolyl, furyl, tetrahydrofuryl, thienyl, and benzothienyl.

"M.p." or "mp" is an abbreviation for melting point; "m.w." or "mw" is an abbreviation for molecular weight.

The compounds of the present invention are made by methods well known to those skilled in the art. The compounds of this invention are generally made from a steroid alcohol starting material, represented by formula (i)



i

wherein a and b are both single bonds and R^2 is hydrogen, or
a is a double bond, b is a single bond and R^2 is hydrogen, or
a is a single bond, b is a double bond and R^2 is absent;
R^1 is -H, aryl, or C_{1-3}alkyl unsubstituted or substituted with aryl and where n is greater than 1, R^1 can be the same or different; R^3 is -H, methyl or ethyl; and n is an integer from zero through 10.

Methods of making starting alcohols of formula (i) are well known to those skilled in the art, and are described, for example, in the following publications: Rasmusson, G.H. et al., J. Med. Chem., 29, 2298-2315 (1986); Rasmusson, G.H. et al., J. Med. Chem., 27, 1690-1701 (1984).

Furthermore, the starting 4-azasteroid-20-alcohols of Formula (i) may be made by several methods well known to those skilled in the art. For example, 4-azasteroids containing a 17-carbonyl group (e.g. carboxaldehyde) may be reacted with the appropriate organo-metallic reagent to yield the corresponding secondary alcohol, while reduction yields the primary alcohol. Also, an appropriate 17-ketone may be reduced (e.g. with sodium borohydride) to the desired alcohol. The above mentioned ketones may be made by several methods well known in the art; one particularly useful method is that of A. Bhattacharya et al., Synthetic Communications 20(17), 2683-2690 (1990), in which an activated carbonyl compound is reacted with a suitable Grignard reagent to give the desired ketone. Other activated carbonyl compounds (e.g. pyridine thioesters) may also be used.

These alcohol functions may be constructed both before and after the formation of the 4-aza moiety.

One method of preparing compounds of formula I is to condense the starting steroid alcohol with an acid of formula (ii)

R^4-COOH (ii)

under conditions known to those skilled in the art, e.g., in an appropriate solvent such as CH_2Cl_2, in the presence of 4-(dimethylamino)-pyridine (DMAP) and N,N'-dicyclohexylcarbodiimide (DCC).

Another method of preparing compounds of formula I is to combine the starting alcohol (i) with an acid chloride of formula (iii) or acid anhydride or mixed anhydride of formula (iv)

R^4–COCl (iii)

$(R^4CO)_2O$ (iv)

under conditions known to those skilled in the art, e.g. under dry conditions using an appropriate solvent such as CH_2Cl_2 at e.g. reduced temperature, such as about 0°C, in the presence of a base such as pyridine.

Carbamate derivatives of formula I can be prepared by reacting the starting alcohol (i) with an isocyanate compound, such as benzyl isocyanate or t–butylisocyanate for example, under conditions known to those skilled in the art, e.g., under dry conditions in an appropriate solvent such as benzene, in the presence of a base such as pyridine or 1,4–diazabicyclo[2.2.2]octane, or in the case of a hindered isocyanate such as t–butylisocyanate, 1,8–diazabicyclo[5.4.0]undec–7–ene (DBU), with heating e.g. to 60°–70°C, or at room temperature.

The thiol esters may be conveniently prepared from the corresponding alcohol via the literature procedure described in Tetrahedron Letters, 22 (1981) pp. 3119–3122, that is, the alcohol and a thiolacid are reacted together in the presence of the preformed adduct from triphenylphosphine and diisopropyl azodicarboxylate.

Alternatively, the free thiol obtained from these thiolesters via standard saponification or reduction methods may then be acylated via standard procedures to obtain other thiolesters.

The variable "R^4" used in the above synthetic method descriptions is defined in formula I, and is independently defined at each occurrence in formula (iv).

Accordingly, the present invention is particularly concerned with providing a method of treating the hyperandrogenic conditions of androgenic alopecia, acne vulgaris, seborrhea, benign prostatic hyperplasia, prostatitis, the prevention and/or treatment of prostatic carcinoma, by oral, parenteral or typical administration, of the novel compounds of the present invention.

The present invention is thus also concerned with providing suitable topical, oral and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention.

The compositions containing the compounds of the present invention as the active ingredient for use in the treatment of e.g., benign prostatic hypertrophy, prostatitis, and prostatic carcinoma, and hyperandrogenic conditions can be administered in a wide variety of therapeutic dosage forms in conventional vehicles for systemic administration, as, for example, by oral administration in the form of tablets, capsules, solutions, or suspensions, of by injection. The daily dosage of the products may be varied over a wide range varying from 0.5 to 1,000

mg per adult human/per day. The compositions are preferably provided in the form of scored tablets containing 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, and 50.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.002 mg. to about 50 mg./kg. of body weight per day. Preferably the range is from about 0.01 mg. to 7 mg./kgs. of body weight per day. These dosages are well below the toxic dose of the product. Capsules containing the product of this invention can be prepared by mixing an active compound of the present invention with lactose and magnesium stearate, calcium stearate, starch, talc, or other carriers, and placing the mixture in gelatin capsule. Tablets may be prepared by mixing the active ingredient with conventional tableting ingredients such as calciuim phosphate, lactose, corn starch or magnesium stearate. The liquid forms in suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methylcellulose and the like. Other dispersing agents which may be employed include glycerin and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservative are employed when intravenous administration is desired.

For the treatment of androgenic alopecia, acne vulgaris, seborrhea, female hirsutism, the compounds of the present invention are administered in a pharmaceutical composition comprising the active compound in combination with a pharmacologically acceptable carrier adapted for topical administration. Parenteral or oral administration are also applicable. These topical pharmaceutical compositions may be in the form of a cream, ointment, gel or aerosol formulation adapted for application to the skin. These topical pharmaceutical compositions containing the compounds of the present invention ordinarily include about 0.1% to 15%, preferably about 5%, of the active compound, in admixture with about 95% of vehicle.

The following examples are illustrative of representative embodiments of this invention and should not be construed to be limits on the scope or spirit of the instant invention.

The fast atom bombardment (FAB) and electron impact (EI) mass spectral (MS) values are reported as molecular ion peaks and are indicated as either M^+, M^{+1}, M^{-1} or M^{+2}, being the molecular weight (mw), the molecular weight plus one atomic mass unit, the molecular weight minus one atomic mass unit, or the molecular weight plus two atomic mass units.

The ^1H nuclear magnetic resonance (NMR) data was taken at 200 or 400 MHz and is tabulated for unique proton values of each compound at the end of the Examples.

Example 1

Preparation of 20-(11-(ethylthio)undecanoyloxy)-4-methyl-5α-4-azapregnan-3-one

To a stirred solution of 20-hydroxy-4-methyl-5α-4-azapregnan-3-one (0.66 g, 2.0 mM), 11-ethylthio-undecanoic acid (0.493 g, 2.0 mM), and 4-(dimethyl-amino)-pyridine (0.242 g, 2.0 mM) in methylene chloride (25 mL) was added N,N'-dicyclohexylcarbo-diimide (0.48 g, 2.3 mM) in methylene chloride (3 mL plus 2x3 mL rinses) at room temperature. After stirring overnight two times, the mixture was filtered from the precipitated dicyclohexylurea and concentrated, and the residue flash chromatographed on silica gel using ethyl acetate as eluant to yield the title compound as a thick oil. MS M^{+1} calculated for $C_{34}H_{59}NO_3S$, mw = 561.90; observed m/e 562.

Example 2

Preparation of 20-ethoxyacetyloxy-4-methyl-5α-4-azapregnan-3-one

Employing substantially the same procedure as described in Example 1, but substituting ethoxyacetic acid in place of the ethylthioundecanoic acid used therein, the title compound is obtained.

Example 3

Preparation of 17-(12-(isopropylthio)dodecanoyloxy)-4-methyl-5α-4-azaandrostan-3-one

Employing substantially the same procedure as described in Example 1, but substituting 17-hydroxy-4-methyl-5α-4-azaandrostan-3-one and 12-(isopropylthio)dodecanoic acid for the 20-hydroxy-4-methyl-5α-4-azapregnan-3-one and 11-ethylthioundecanoic acid, respectively, used therein, the title compound was obtained. MS M^+ calculated for $C_{34}H_{59}NO_3S$, mw = 561.92; observed m/e 561.

Example 4

Preparation of a) 20-(9-(isopropylthio)nonanoyloxy)-5α-4-azapregnan-3-one and
b) 20-(12-(isopropylthio)dodecanoyloxy)-5α-4-azapregn-1-ene-3-one

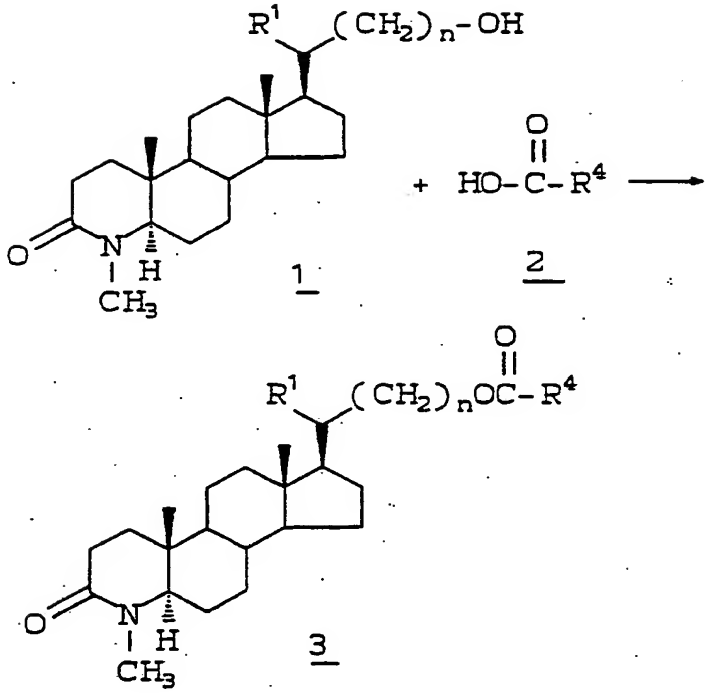
Employing substantially the same procedure as described in Example 1, but substituting the steroid alcohol and acid starting materials used therein with the following compounds, both of the title compounds were obtained:

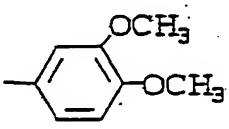
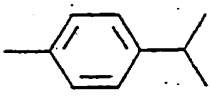
Title compound a): 20-hydroxy-5α-4-azapregnan-3-one and 9-(isopropylthio)nonanoic acid. MS M^+ calculated for $C_{32}H_{55}NO_3S$, mw = 533.85; observed m/e 533;

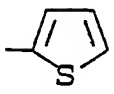
Title compound b): 20-hydroxy-5α-4-azapregn-1-ene-3-one and 12-(isopropylthio)dodecanoic acid. MS M^+ calculated for $C_{35}H_{59}NO_3S$, mw = 573.92; observed m/e 573.

Example 5

Compounds of formula 3, below, were made employing substantially the same procedure as described in Example 1, but substituting the compounds of formula 1 and 2, below, in place of the 20-hydroxy-4-methyl-5α-4-azapregnan-3-one and 11-ethylthioundecanoic acid respectively, used therein.


R1
(CH2)n-OH
O
HO-C-R4
N
H
CH3
1
2
O
R1
(CH2)nOC-R4
N
H
CH3
3

	R^1	n	R^4
a)	$-CH_3$	zero	$-(CH_2)_{11}CH_3$
b)	$-CH_3$	zero	$-CH_2CH(CH_3)CH_2CH_2CH=C(CH_3)_2$
c)	$-CH_3$	zero	$-CH_2$-1-adamantyl
d)	$-CH_3$	zero	$-CH_2$-2-norbornyl
e)	$-CH_3$	zero	
f)	$-CH_3$	zero	
g)	$-CH_3$	zero	$-CH_2-S-CH(CH_3)_2$
h)	$-CH_3$	zero	$-(CH_2)_8-S-CH(CH_3)_2$

	R^1	n	R^4 (CONT D)
i)	$-CH_3$	zero	$-(CH_2)_{11}-S-CH(CH_3)_2$
j)	$-CH_3$	zero	$-(CH_2)_{11}-S-C(CH_3)_3$
k)	$-CH_3$	zero	$-(CH_2)_3$ 
l)	$-CH_3$	1	$-(CH_2)_{11}-S-CH(CH_3)_2$
m)	$-H$	zero	$-CH(C_2H_5)-CH_2CH_2CH_2CH_3$
n)	$-H$	zero	$-(CH_2)_{11}-S-CH(CH_3)_2$

The compounds above have the following corresponding mass spectral data:

a) MS M^+ calculated for $C_{34}H_{59}NO_3$, mw=529.85; observed m/e 529;
b) MS M^+ calculated for $C_{31}H_{51}NO_3$, mw=485.75; observed m/e 485;
c) MS M^+ calculated for $C_{33}H_{51}NO_3$, mw=509.78; observed m/e 509;
d) MS M^+ calculated for $C_{30}H_{47}NO_3$, mw=469.71; observed m/e 469;
e) MS M^+ calculated for $C_{31}H_{45}NO_5$; mw=511.71; observed m/e 511;
f) MS M^+ calculated for $C_{31}H_{45}NO_3$; mw=479.71; observed m/e 479;
g) MS M^+ calculated for $C_{26}H_{43}NO_3S$; mw=449.69; observed m/e 449;
h) MS M^+ calculated for $C_{33}H_{57}NO_3S$; mw=547.88; observed m/e 548;
i) MS M^+ calculated for $C_{36}H_{63}NO_3S$; mw=589.94; observed m/e 589;
j) MS M^{+1} calculated for $C_{37}H_{65}NO_3S$; mw=604.00; observed m/e 605;
k) MS M^{+1} calculated for $C_{29}H_{43}NO_3S$; mw=485.73; observed m/e 486;
l) MS M^{-1} calculated for $C_{37}H_{65}NO_3S$; mw=604.00; observed m/e 603;
m) MS M^+ calculated for $C_{28}H_{47}NO_3$; mw=445.69; observed m/e 445;
n) MS M^+ calculated for $C_{35}H_{51}NO_3S$; mw=575.92; observed m/e 575.

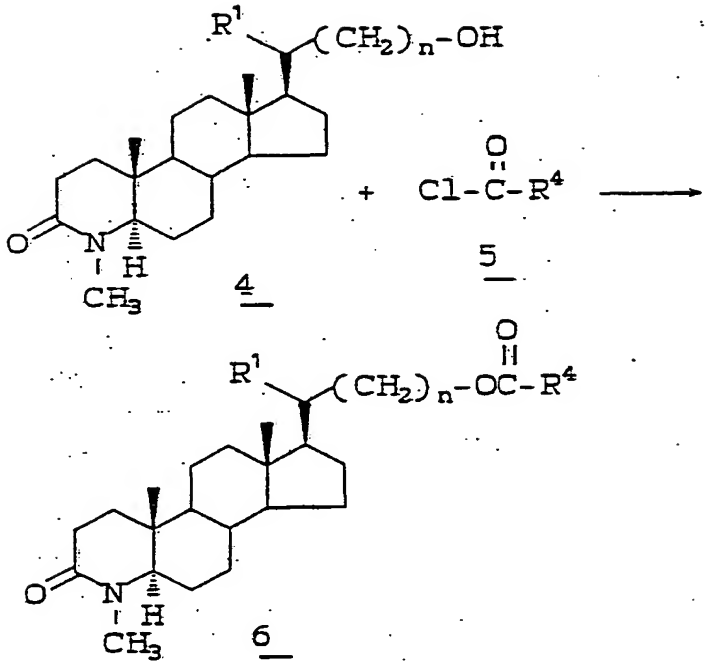
Example 6

Preparation of 4-methyl-20-(10-undecenoyloxy)-5α-4-azapregnan-3-one

To a solution of 20-hydroxy-4-methyl-5α-4-azapregnan-3-one (0.167 g, 0.5 mM) and pyridine (0.1 mL) in anhydrous methylene chloride (4.5 mL) at ice-bath temperatures was added 10-undecenoyl chloride (0.13 mL, 0.6 mM) dropwise. After 10 minutes, the reaction mixture was allowed to warm to room temperature and stir overnight. After diluting further with methylene chloride the mixture was washed with dilute hydrochloric acid, water, and brine, and dried (Na_2SO_4). The residue obtained from concentration of the filtered solution was flash chromatographed on silica gel using ethyl acetate as eluant to give the title compound as a glaze. MS M^+ calculated for $C_{32}H_{53}NO_3$, mw = 499.78; observed m/e 499.

Example 7

Compounds of formula 6, below, were made employing substantially the same procedure as described in Example 6, but substituting the compounds of formula 4 and 5, below, in place of the 20-hydroxy-4-methyl-5α-4-azapregnan-3-one and 10-undecenoyl chloride, respectively, used therein.



4 5 6

	R^1	n	R^4
a)	$-CH_3$	zero	$-CH_2C(CH_3)_3$
b)	$-CH_3$	zero	$-C(CH_3)_3$
c)	$-CH_3$	zero	$-(CH_2)_{10}COOCH_3$
d)	$-CH_3$	zero	$-CH_2CH_2COOCH_2$-Ph
e)	$-CH_3$	1	$-CH_3$
f)	$-CH_3$	1	$-C(CH_3)_3$
g)	-H	zero	$-CH_3$
h)	-H	zero	$-C(CH_3)_3$

The compounds above have the following corresponding mass spectral data:

a) MS M^+ calculated for $C_{27}H_{45}NO_3$, mw=431.67; observed m/e 431;
b) MS M^{+1} calculated for $C_{26}H_{43}NO_3$, mw=417.64; observed m/e 418;
c) MS M^+ calculated for $C_{34}H_{57}NO_5$; mw=559.84; observed m/e 559;
d) MS M^{+2} calculated for $C_{32}H_{45}NO_5$; mw=523.72; observed m/e 525;
e) MS M^+ calculated for $C_{24}H_{39}NO_3$; mw=389.59; observed m/e 389;
f) MS M^+ calculated for $C_{27}H_{45}NO_3$; mw=431.67; observed m/e 431;
g) MS M^+ calculated for $C_{22}H_{35}NO_3$; mw=361.53; observed m/e 361;
h) MS M^+ calculated for $C_{25}H_{41}NO_3$; mw=403.61; observed m/e 403.

Example 8

Preparation of 20-trimethylacetyloxy-5α-4-azapregn-1-ene-3-one

Employing substantially the same procedure as described in Example 6, but substituting 20-hydroxy-5α-4-azapregn-1-ene-3-one and trimethylacetyl chloride for the 20-hydroxy-4-methyl-5α-4-azapregnan-3-one and 10-undecenoyl chloride, respectively, used therein, the title compound was obtained. MS M^{-1} calculated for $C_{25}H_{39}NO_3$, mw = 402.53; observed m/e 401.

Example 9

Preparation of 20-(11-(ethylsulfinyl)undecanoyloxy)-4-methyl-5α-4-azapregnan-3-one

To a stirred solution of 20-(11-(ethylthio)-undecanoyloxy)-4-methyl-5α-4-azapregnan-3-one (0.056 g, 0.1 mM) in acetone (5 mL) at room temperature was added a solution of sodium periodate (0.033 mg, 0.154mM) in water (3 drops). After prolonged stirring with additional portions of the periodate added (0.046 g total) over 3 days, the solvents were removed in vacuo, and the residue extracted with methylene chloride. The methylene chloride was removed in vacuo, and the resulting residue was flash chromatographed on silica gel (30% acetone/methylene chloride eluant) to give the title compound as a glaze. MS M^+ calculated for $C_{34}H_{59}NO_4S$, mw = 577.90; observed m/e 577.

Example 10

Preparation of 17ß-(benzylaminocarbonyloxy)-4-methyl-5α-4-azaandrostan-3-one

To a solution of 17ß-hydroxy-4-methyl-5α-4-azaandrostan-3-one (61 mg) in pyridine (0.60 ml) was added benzyl isocyanate (54 mg, 0.40 mmol). The mixture was stirred at 60-70°C under N_2 for 18 hr and pumped in vacuo to remove pyridine. The residue was purified using a silica gel plate (2000 µ) developed with ethyl acetate (Rf = 0.37, run in EtOAc) to give the title compound; m.p. is 216-217°C.

Example 11

Preparation of 20-(3-carboxypropionyloxy)-4-methyl-5α-4-azapregnan-3-one

20-(3-(Carbobenzyloxy)propionyloxy)-4-methyl-5α-4-azapregnan-3-one (0.05 g, 0.095 mM) was reduced with hydrogen in ethyl acetate in the presence of 5% palladium on carbon, to obtain the title compound. MS M^{+1} calculated for $C_{25}H_{39}NO_5$, mw=433.64; observed m/e 434.

Example 12

Preparation of 20-(acetylthiomethyl)-4-methyl-5α-4-azapregnan-3-one

By reacting 20-(hydroxymethyl)-4-methyl-5α-4-azapregnan-3-one with thiolacetic acid as per the procedure of Tetrahedron Letters 22 (1981) pp. 3119-3122, the title compound is obtained.

Example 13

Preparation of 17-(t-butylaminocarbonyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one

To a stirred solution of 17-(hydroxymethyl)-4-methyl-5α-4-azaandrostan-3-one (0.048 g, 0.15 mM) in dried benzene (5 mL) was added at room temperature t-butylisocyanate (0.03 mL, 0.23mM) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.023 mL, 0.15 mM). After stirring for two days, the volatiles

were removed in vacuo and the residue flash chromatographed on silica gel using ethyl acetate as eluant to give the title compound as a white solid. MS M^{+1} calculated for $C_{25}H_{42}N_2O_3$, mw = 418.55; observed m/e 419.

Example 14

Preparation of 20-(t-butylaminocarbonyloxy)-4-methyl-5α-4-azapregnan-3-one

Employing substantially the same procedure as described in Example 13, but substituting 20-hydroxy-4-methyl-5α-4-azapregnan-3-one for the steroid alcohol used therein, the title compound was obtained. MS M^{+1} calculated for $C_{26}H_{44}N_2O_3$, mw = 432.65; observed m/e 433.

Example 15

Preparation of 17-(methylaminocarbonyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one

Employing substantially the same procedure as described in Example 10, but substituting methyl isocyanate and 17-(hydroxymethyl)-4-methyl-5α-4-azaandrostan-3-one for the benzyl isocyanate and steroid alcohol, respectively, used therein, the title compound was obtained. MS M^{+2} calculated for $C_{22}H_{36}N_2O_3$, mw = 376.54; observed m/e 378.

Also included with the scope of this invention are 4-N-X analogs where X is OH, NH_2 or SCH_3. The 4-N-OH and 4-N-NH_2 derivatives can be made by incorporating hydroxylamine or hydrazine, respectively, in place of methyl amine in the seco acid ring A closure for the starting androstanes herein as described in J. Med. Chem. 29, 2998-2315 (1986) by Rasmusson et al. Further, reaction of the anion of the saturated 4-N-H androstanes, wherein the anion is generated from the 4-NH precursor by sodium hydride, and methylsulfenyl chloride can produce the corresponding 4-N-SCH_3 derivative. Thus, substituent R^3 on the 4-N position also includes OH, NH_2 and SCH_3.

NMR DATA (ppm)

Example	Angular Methyls	Miscellaneous
1	0.64, 0.88	2.94 (-4-NC$\underline{H}_3$)
3	0.81, 0.91	1.24 (-SCH(C$\underline{H}_3$)$_2$) 1.28
4a	0.64, 0.90	1.25 (-SCH(C$\underline{H}_3$)$_2$) 1.28
4b	0.64, 0.94	1.22 (-SCH(C$\underline{H}_3$)$_2$) 1.26
5a	0.64, 0.88	2.95 (-4-NC$\underline{H}_3$)
5b	0.62, 0.86	2.92 (-4-NC$\underline{H}_3$)
5c	0.62, 0.87	2.92 (-4-NC$\underline{H}_3$)
5d	0.64, 0.88	2.92 (-4-NC$\underline{H}_3$)
5e	0.59, 0.88	3.80 (Ph-(OC$\underline{H}_3$)$_2$) (Split)
5f	0.65, 0.82	1.22 (Ph-CH(C$\underline{H}_3$)$_2$) 1.25
5g	0.65, 0.88	3.21 (-SC$\underline{H}_2$CO$_2$-)
5h	0.63, 0.88	1.24 (-SCH(C$\underline{H}_3$)$_2$) 1.28
5i	0.63, 0.87	1.24 (-SCH(C$\underline{H}_3$)$_2$) 1.27
5j	0.64, 0.88	1.30 (-C(C$\underline{H}_3$)$_3$
5k	0.64, 0.88	2.92 (-4-NC$\underline{H}_3$)
5l	0.70, 0.88	1.24 (-SCH(C$\underline{H}_3$)$_2$) 1.26

NMR DATA (ppm) con't

Example	Angular Methyls	Miscellaneous
5m	0.63, 0.85	2.89 (-4-NC$\underline{H}_3$)
5n	0.67, 0.89	2.93 (-4-NC$\underline{H}_3$)
6	0.64, 0.88	2.92 (-4-NC$\underline{H}_3$)
7a	0.64, 0.88	1.02 (-C(C$\underline{H}_3$)$_3$)
7b	0.64, 0.87	1.13 (-C(C$\underline{H}_3$)$_3$)
7c	0.64, 0.88	3.66 (-CO$_2$C$\underline{H}_3$)
7d	0.62, 0.87	5.14 (-OC$\underline{H}_2$Ph)
7e	0.69, 0.88	2.04 (-OCOC$\underline{H}_3$)
7f	0.70, 0.88	1.20 (-C(C$\underline{H}_3$)$_3$)
7g	0.66, 0.90	2.02 (-OCOC$\underline{H}_3$)
7h	0.68, 0.89	1.18 (-C(C$\underline{H}_3$)$_3$)
8	0.64, 0.94	1.16 (-C(C$\underline{H}_3$)$_3$)
9	0.62, 0.88	2.94 (-4-NC$\underline{H}_3$)
10	0.89, 0.92	2.94 (-4-NC$\underline{H}_3$)
11	0.62, 0.86	2.92 (-4-NC$\underline{H}_3$)
13	0.64, 0.86	1.29 (-OCONH-C(C$\underline{H}_3$)$_3$)
14	0.69, 0.89	1.32 (-OCONH-C(C$\underline{H}_3$)$_3$)
15	0.67, 0.88	2.78 (-OCONH-C$\underline{H}_3$) 2.82

Novel compounds of the present invention further include, but are not limited to, the following compounds:

20-(t-butylaminocarbonyloxy)-4-methyl-5-α-4-aza-pregnan-3-one,

20-(isopropylaminocarbonyloxy)-4-methyl-5-α-4-aza-pregnan-3-one,

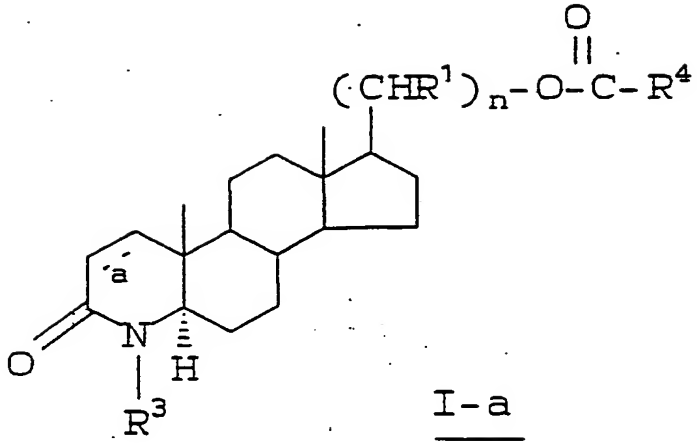
17-((2-ethylphenylamino)carbonyloxymethyl)-4-methyl-5-α-4-azaandrostan-3-one,

4-methyl-20-(methylaminocarbonyloxy)-5-α-4-aza-pregnan-3-one, and

24-(t-butylaminocarbonyloxy)-4-methyl-5-α-4-aza-cholan-3-one.

These compounds can be prepared using substantially the same procedures as described in Example 14, using the appropriate starting materials.

Furthermore, the present invention discloses compounds of formula I-a, useful for dually inhibiting both steroid 5α-reductase enzymes 1 and 2 and selectively inhibiting 5α-reductase 1,



I-a

wherein:

(I) a is single bond;

R^1 is H;

R^3 is -H, methyl, ethyl, -OH, $-NH_2$, or $-SCH_3$;

n is an integer selected from 1 through 10; and

R^4 is 1) $-C_{1-6}$ alkyl substituted with an unsubstituted phenyl ring,
2) unsubstituted C_{5-10} cycloalkyl,
3) unsubstituted phenyl,
4) amino,
5) $-C_{1-8}$ alkyl substituted amino, or
6 $-C_{1-8}$ alkoxy;

(II) a is a single bond;

R^3 is -H;

n is zero; and

R^4 is $-CH_3$; or

(III) a is a single bond;
R^1 is $-CH_3$;
R^3 is -H;
n is 1; and
R^4 is $-CH_3$;

or a pharmaceutically acceptable salt or ester thereof.

BIOLOGICAL ASSAYS

Preparation of Human prostatic and scalp 5α-reductases

Samples of human tissue were pulverized using a freezer mill and homogenized in 40 mM potassium phosphate, pH 6.5, 5 mM magnesium sulfate, 25 mM potassium chloride, 1 mM phenylmethylsulfonyl fluoride, 1 mM dithiothreitol (DTT) containing 0.25 M sucrose using a Potter-Elvehjem homogenizer. A crude nuclear pellet was prepared by centrifugation of the homogenate at 1,500xg for 15 min. The crude nuclear pellet was washed two times and resuspended in two volumes of buffer. Glycerol was added to the resuspended pellet to a final concentration of 20%. The enzyme suspension was frozen in aliquots at -80°C. The prostatic and scalp reductases were stable for at least 4 months when stored under these conditions.

5α-reductase assay.

The reaction mixture contained in a final volume of 100 µl is: 40 mM buffer (human scalp, potassium phosphate, pH 6.5; human prostatic 5α-reductase, sodium citrate, pH 5.5), 0.3-10 µM ^{14}C-T (or ^{3}H-T) ("T" stands for testosterone), 1 mM DTT, and 500 µM NADPH. Typically, the assay was initiated by the addition of 50-100 µg prostatic homogenate or 75-200 µg scalp homogenate and incubated at 37°C. After 10-50 min the reaction was quenched by extraction with 250 µl of a mixture of 70% cyclohexane: 30% ethyl acetate containing 10 µg each DHT and T. The aqueous and organic layers were separated by centrifugation at 14,000 rpm in an Eppendorf microfuge. The organic layer was subjected to normal phase HPLC (10 cm Whatman partisil 5 silica column equilibrated in 1 ml/min 70% cyclohexane: 30% ethyl acetate; retention times: DHT, 6.8-7.2 min; androstanediol, 7.6-8.0 min; T, 9.1-9.7 min). The HPLC system consisted of a Waters Model 680 Gradient System equipped with a Hitachi Model 655A auto-sampler, Applied Biosystems Model 757 variable UV detector, and a Radiomatic Model A120 radioactivity analyzer. The conversion of T to DHT was monitored using the radioactivity flow detector by mixing the HPLC effluent with one volume of Flo Scint 1 (Radiomatic). Under the conditions described, the production of DHT was linear for at least 25 min. The only steroids observed with the human prostate and scalp preparations were T, DHT and androstanediol.

Stumptail macaque protocol

The following protocol is utilized with the stumptail macaque monkey to demonstrate the effect of compounds of the present invention for promoting hair growth.

Twenty-one male stumptail macaque monkeys of species Macaca speciosa are assigned to vehicle control and drug treatment groups on the basis of baseline hair weight data. This assignment procedure is necessary to insure that the average baseline hair growth for each control and experimental group is comparable. The control and drug treatment groups are as follows:

1. Topical 50:30:20 vehicle (N = 6)
2. Oral 5α-reductase and topical 50:30:20 vehicle (N = 5)
3. Oral placebo (N = 5)
4. 5α-reductase in vehicle (N = 5)

The vehicle consists of 50% propylene glycol, 30% ethanol and 20% water. A 100 mM concentration of topical 5α-reductase is formulated in this vehicle. The same 5α-reductase is administered as an oral dose of 0.5 mg per monkey. Immediately prior to the dosing phase of the study, hair is removed from a 1 inch square area (identified by four tatoos) in the center of the balding scalp. This hair collection is the baseline hair growth determination prior to the beginning of treatment. Approximately 250 µL of vehicle and 5α-reductase in vehicle is prepared and topically administered to the

tatooed area of the scalp, The selected 5α-reductase and placebo is ingested by the monkeys at the same time as the topical doses are administered. The monkeys are dosed once per day, seven days per week for twenty weeks.

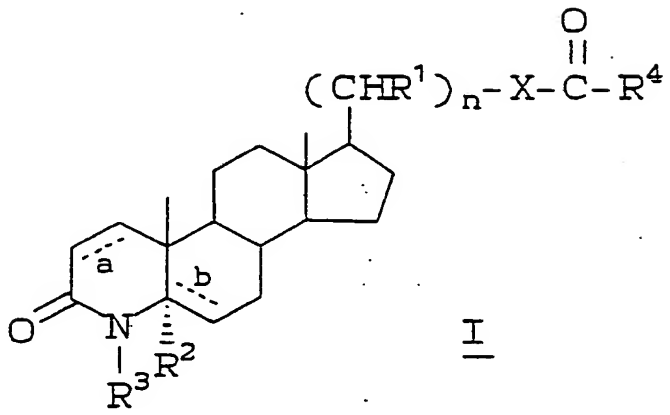
At four week intervals throughout the dosing phase of the study, each monkey is shaved and the hair is collected and weighed. The body weight data (at baseline and during assay) is analyzed by the monparametric Wilcoxon rank-sum test. Differences are significant at $p < 0.05$. Hair weight data at each week collection for vehicle, placebo and treatment groups are expressed as the change from baseline. Statistical analysis is performed on the rank of the data to show overall differences among groups at each four week collection.

While the invention has been described and illustrated with reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode

of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of formula I



I

wherein a and b are both single bonds and R^2 is hydrogen, or
a is a double bond, b is a single bond and R^2 is hydrogen, or
a is a single bond, b is a double bond and R^2 is absent;

R^1 can be the same or different at each occurrence when n is greater than 1 and is selected from: -H, aryl, or $-C_{1-3}$alkyl unsubstituted or substituted with aryl;

R^3 is -H, methyl, ethyl, -OH, $-NH_2$, or $-SCH_3$;

n is an integer selected from zero through 10;

X is -O- or -S-; and

R^4 is 1) $-C_{1-20}$ alkyl, unsubstituted or substituted with one or more of:
a) -OH,
b) halo,
c) $-C_{1-8}$ alkoxy,
d) $-C_{1-6}$ alkenyl,

e) $-CONR^5R^5$, wherein R^5 is independently
   i) -H,
   ii) $-C_{1-8}$ alkyl unsubstituted or substituted with one or more of R^7, aryl or heterocycle, the aryl being unsubstituted or substituted with one or more of R^7 or R^9,
   iii) aryl unsubstituted or substituted with one or more of R^7 or R^9, or
   iv) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9,

f) $-COOR^6$, wherein R^6 is
   i) -H,
   ii) $-C_{1-8}$ alkyl unsubstituted or substituted with one or more of R^7 or aryl, the aryl being unsubstituted or substituted with one or more of R^7 or R^9, or
   iii) aryl, unsubstituted or substituted with one or more of R^7 or R^9,

g) $-S(O)_p-R^5$, wherein p is zero, 1 or 2;

h) $-N(R^5)_2$,

i) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9,

j) heterocycle, unsubstituted or substituted with one or more of R^7 or R^9,

k) $-C_{3-10}$ cycloalkyl, unsubstituted or substituted with one or more of R^7 or R^9, or

1) $-CONR^8-CO-NHR^8$, wherein R^8 is -H, $-C_{1-8}$ alkyl, benzyl or cyclohexyl,

2) aryl, unsubstituted or substituted with one or more of aryl, R^7 or R^9,

3) heterocycle or $-C_{3-10}$ cycloalkyl, either of which is unsubstituted or substituted with one or more of R^7 or R^9,

4) $-NR^5R^5$, or

5) $-OR^5$;

R^7 is

1) -OH,

2) $-C_{1-3}$ alkoxy,

3) -CN,

4) $-COOR^6$

5) $-C_{1-8}$alkyl-$COOR^6$

6) $-NO_2$, or

7) halo; and

8) amino, mono C_1-C_4alkylamino, di-C_1-C_4-alkylamino;

R^9 is

1) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or more of aryl or R^7,

2) -CO-A, $-C_{1-8}$ alkyl-CO-A, -NHCO-A, or $-S(O)_p$-A, wherein p is defined above and A is

a) -H,

b) $-C_{1-8}$ alkyl, unsubstituted or substituted with one or more of
   i) $-R^7$, or
   ii) aryl, unsubstituted or substituted with one or more of R^7, or

c) aryl, unsubstituted or substituted with one or more of R^7,

3) -NHCO-heterocycle,

4) $-N(R^{10})_2$ or $-CON(R^{10})_2$ wherein R^{10} is independently, heterocycle or -A,

5) $-NHCO-(CH_2)_q-CO-Q$, wherein q is 1-4, and Q is $-N(R^{10})_2$ or $-OR^{10}$;

with the provisos that:

when n is 1-10, b is a single bond, R^1 is -H at each occurrence, X is -O-, and R^4 is $-C_{1-6}$alkyl, R^4 is not substituted with an unsubstituted phenyl ring;

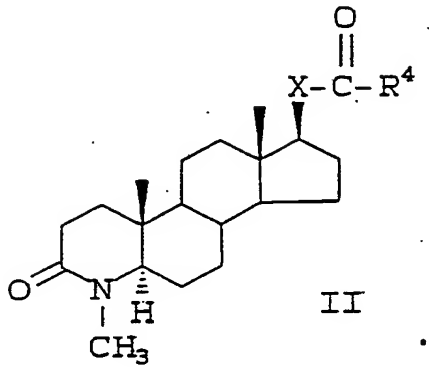
when n is 1-10, b is a single bond, R^1 is -H at each occurrence, and X is -O-, R^4 is not unsubstituted C_{5-10}cycloalkyl, unsubstituted phenyl, amino, $-C_{1-8}$alkyl substituted amino, or $-C_{1-8}$alkoxy;

when n is zero, X is -O-, a and b are both single bonds and R^3 is -H, then R^4 is not $-CH_3$; and

when n is 1, R^1 is $-CH_3$, X is -O-, a and b are both single bonds, and R^3 is -H, then R^4 is not $-CH_3$;

or a pharmaceutically acceptable salt or ester the thereof.

2. The compound of Claim 1 having structural formula II



II

3. The compound of Claim 2 wherein R^4 is $-C_{1-20}$alkyl, unsubstituted or substituted with one or more of

$-OH$, halo, $-C_{1-8}$alkoxy, $-C_{1-6}$alkenyl, $-S(O)_p-R^5$, $-N(R^5)_2$, aryl unsubstituted or substituted with one or more of aryl, R^7or R^9, heterocycle unsubstituted or substituted with one or more of R^7 or R^9, or $-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9.

4. The compound of Claim 2 wherein R^4 is $-C_{1-20}$ alkyl substituted with $-CONR^5R^5$, $-COOR^6$ or $-CONR^8CONHR^8$.

5. The compound of Claim 2 wherein R^4 is

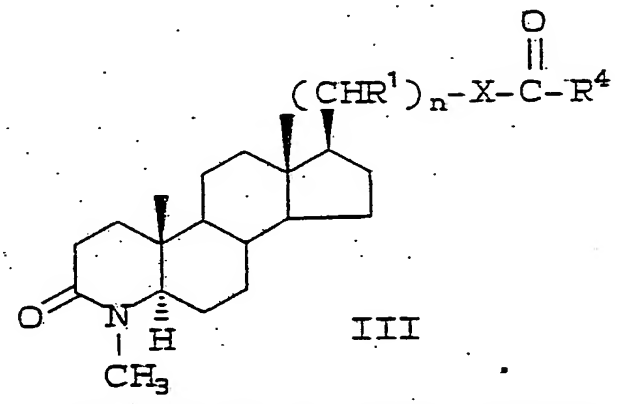
aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9;

heterocycle unsubstituted or substituted with one or more of R^7 or R^9;

$-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9;

$-NR^5R^5$; or $-OR^5$.

6. The compound of Claim 1 having structural formula III



III

7. The compound of Claim 6 wherein R^4 is $-C_{1-20}$ alkyl, unsubstituted or substituted with one or more of

-OH, halo, $-C_{1-8}$alkoxy, $-C_{1-6}$alkenyl, $-S(O)_p-R^5$, $-N(R^5)_2$, aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9, heterocycle unsubstituted or substituted with one or more of R^7 or R^9, or $-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9.

8. The compound of Claim 6 wherein R^4 is $-C_{1-20}$ alkyl substituted with $-CONR^5R^5$, $-COOR^6$ or $-CONR^8CONHR^8$.

9. The compound of Claim 6 wherein R^4 is

aryl unsubstituted or substituted with one or more of aryl, R^7 or R^9;

heterocycle unsubstituted or substituted with one or more of R^7 or R^9;

$-C_{3-10}$ cycloalkyl unsubstituted or substituted with one or more of R^7 or R^9;

$-NR^5R^5$; or $-OR^5$.

10. A compound selected from the group consisting of:

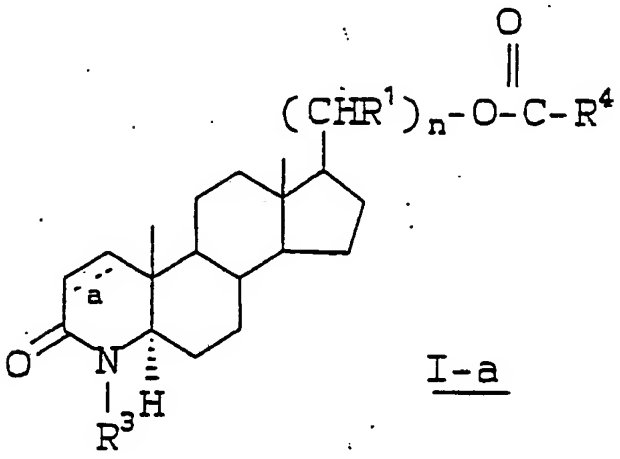
20-(11-(ethylthio)undecanoyloxy)-4-methyl-5α-4-azapregnan-3-one,
20-ethoxyacetyloxy-4-methyl-5α-4-azapregnan-3-one,
17-(12-(isopropylthio)dodecanoyloxy)-4-methyl-5α-4-azaandrostan-3-one,
20-(12-(isopropylthio)-dodecanoyloxy)-5α-4-azapregn-1-ene-3-one,
17-acetyloxymethyl-4-methyl-5α-4-azaandrostan-3-one,
4-methyl-20-tridecanoyloxy-5α-4-azapregnan-3-one,
20-t-butylacetyloxy-4-methyl-5α-4-azapregnan-3-one,
4-methyl-20-trimethylacetyloxy-5α-4-azapregnan-3-one,
4-methyl-20-(10-undecenoyloxy)-5α-4-azapregnan-3-one,
20-(3,7-dimethyl-6-octenoyloxy)-4-methyl-5α-aza-pregnan-3-one,
20-(3-carboxypropionyloxy)-4-methyl-5α-4-azapregnan-3-one,
20-(11-(carbomethoxy)undecanoyloxy)-4-methyl-5α-4-azapregnan-3-one,
20-(3-(carbobenzyloxy)propionyloxy)-4-methyl-5α-4-azapregnan-3-one,
20-(1-adamantylacetyloxy)-4-methyl-5α-4-azapregnan-3-one

4-methyl-20-(2-norbornylacetyloxy)-5α-4-azapregnan-3-one,
20-(3,4-dimethoxyphenyl)acetyloxy-4-methyl-5α-4-aza-pregnan-3-one,
20-(4-isopropylphenyl)acetyloxy-4-methyl-5α-4-aza pregnan-3-one
20-(isopropylthio)acetyloxy-4-methyl-5α-4-aza-pregnan-3-one,
20-(9-(isopropylthio)nonanoyloxy)-4-methyl-5α-4-aza-pregnan-3-one,
20-(12-(isopropylthio)dodecanoyloxy)-4-methyl-5α-4-azapregnan-3-one,
20-(11-(ethylsulfinyl)undecanoyloxy)-4-methyl-5α-4-azapregnan-3-one,
20-(12-(t-butylthio)dodecanoyloxy)-4-methyl-5α-4-aza-pregnan-3-one
4-methyl-20-(4-thien-2-yl)butyryloxy-5α-4-aza-pregnan-3-one,
20-trimethylacetyloxy-5α-4-azapregnan-3-one,
20-(9-(isopropylthio)nonanoyloxy)-5α-4-azapregnan-3-one,
20-(12-(isopropylthio)dodecanoyloxy)-5α-4-azapregnan-3-one,
20-acetoxymethyl-4-methyl-5α-4-azapregnan-3-one,
4-methyl-20-(trimethylacetyloxy)methyl-5α-4-aza-pregnan-3-one,
20-(12-(isopropylthio)dodecanoyloxy)methyl-4-methyl-5α-4-azapregnan-3-one,
4-methyl-17-trimethylacetyloxymethyl-5α-4-azaandrostan-3-one,
17-(2-ethylhexanoyloxy)methyl-4-methyl-5α-4-azaandrostan3-one,

17-(12-(isopropylthio)dodecanoyloxy)methyl-4-methyl-5α-4-azaandrostan-3-one,
17ß-(benzylaminocarbonyloxy)-4-methyl-5α-4-azaandrostan-3-one, and
20-trimethylacetyloxy-5α-4-azapregn-1-ene-3-one,

or a pharmaceutically acceptable salt or ester thereof.

11. A compound of formula I-a



I-a

wherein:
(I) a is a single or double bond;
R^1 is -H;
R^3 is -H, methyl, ethyl, -OH, $-NH_2$, or $-SCH_3$;
n is an integer seleted from 1 through 10; and

R^4 is
1) $-C_{1-6}$ alkyl substituted with an unsubstituted phenyl ring,
2) unsubstituted C_{5-10} cycloalkyl,
3) unsubstituted phenyl,
4) amino,
5) $-C_{1-8}$ alkyl substituted amino, or

(II) a is a single bond;
R^3 is -H;
n is zero; and
R^4 is $-CH_3$; or

(III) a is a single bond;
R^1 is $-CH_3$;
R^3 is -H;
n is 1; and
R^4 is $-CH_3$;

or a pharmaceutically acceptable salt or ester thereof.

12. A compound selected from the group consisting of:

17-(t-butylaminocarbonyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one,
17-(methylaminocarbonyloxymethyl)-4-methyl-5α-4-azaandrostan-3-one, and
20-(t-butylaminocarbonyloxy)-4-methyl-5α-4-azapregnan-3-one,

or a pharmaceutically acceptable salt or ester thereof.

13. A compound selected from the group consisting of:

20-(t-butylaminocarbonyloxy)-4-methyl-5-α-4-aza-pregnan-3-one,

20-(isopropylaminocarbonyloxy)-4-methyl-5-α-4-aza-pregnan-3-one,

17-((2-ethylphenylamino)carbonyloxymethyl)-4-methyl-5-α-4-azaandrostan-3-one,

4-methyl-20-(methylaminocarbonyloxy)-5-α-4-aza-pregnan-3-one, and

24-(t-butylaminocarbonyloxy)-4-methyl-5-α-4-aza-cholan-3-one,

or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in a pharmaceutically acceptable carrier therefor.

15. The use of a compound of Claim 1 for the preparation of a medicament useful for treating benign prostatic hyperplasia, acne, female hirsutism, male pattern baldness, androgenic alopecia, prostatitis, and/or preventing prostatic carcinoma in a human host in need of such treatment.

16. The method of Claim 15 wherein said compound is an inhibitor of 5α-reductase 1.

17. The method of Claim 15 wherein said compound is an inhibitor of 5α-reductase 2.

18. The method of Claim 15 wherein said compound is a dual inhibitor of both 5α-reductase 1 and 2.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/04771

A. CLASSIFICATION OF SUBJECT MATTER
IPC(5) :A61K 31/435 C07D 221/02
US CL :546/77; 514/284
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : A61K 31/470

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS Online Structure Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Jour. Clinical Endoc. and METAB., Vol. 74 1992, Diani et al. "HAIR GROWTH EFFECTS OF ORAL ADMINISTRATION OF FINASTERIDE, A, steroid 5 Reductase Inhibitor, alone and in combination with Topical Minoxidil in the Balding Stumptail Macaque, pages 345-350. See page 345, para. bridging cols 1-2, last 3 lines. See entire document.	15-18
A	J. ORG. CHEM. Vol. 46, 1981, BACK "OXIDATION OF AZASTEROID LASCTASMS AND ALCOHOLS WITH BENZENESELENIC ANHYDRIDE' PAGES 1442-6. See entire document.	1-18

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
13 JULY 1993

Date of mailing of the international search report
31 AUG 1993

Name and mailing address of the ISA/US
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Washington, D.C. 20231

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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/04771

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Jour. MED. CHEM. Vol. 27, 1984, Rasmusson et al "AZASTEROIDS AS INHIBITORS OF RAT PROSTATIC 5 REDUCTASE" pages 1690-1701. See entire document.	1-18
A	Jour. MED. CHEM. Vol. 29, 1986, Rasmusson et al "AZASTEROIDS STRUCTURE ACTIVITY RELATIONSHIPS FOR INHIBITION OF 5 REDUCTASE AND OF ANDROGEN RECEPTOR BINDING" Pages 2298-2315. See entire document.	1-18
A	E,P, B 0200858 (Cainelli et al.) 12 November 1986. See entire doucment.	1-18
Y	U.S. A, 4377584 (Rasmusson et al.) 22 March 1983. See Col. 13, No. 19, 21, etc. See entire document.	1-3, 6-7, 10-11, 13-17
A	U.S. A, 4760071 (Rasmusson et al) 26 July 1988. See entire document.	1-18
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X	STEROIDS Vol. 47, 1986, Brooks et al. "5 Reductase Inhibitory and Antiandrogenic Activities of Some 4 Azasteroids in The Rat" pages 1-19. See page 5.	1, 13-17
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INTERNATIONAL SEARCH REPORT

International application No.
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Jour. Pharm. Sci., Vol. 62, 1973, Doorenbos et al. "Synthesis' and Antimicrobial Properties of 17B Isopreviyloxy-4 Axa 5 Androstane and the 4 Methyl Derivative" pages 638-40. See entire article.	1-3,6-7, 10-11

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